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**to**

**The National Toxicology Program**

**- Appendix 4 -**

**Commentary on the Results of the  
IARC Multi-Center Study,  
“Lung Cancer and Exposure to Environmental Tobacco Smoke,”  
Published in the IARC Biennial (1996-1997) Report**

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Results from the International Agency for Research on Cancer (IARC) multi-center epidemiologic study of environmental tobacco smoke (ETS) exposure and lung cancer risk were recently published for the first time in the IARC Biennial Report for 1996-1997 (IARC, 1997; see Tab A, section 3.7.2). This study, which began in 1988, represents the largest study in Europe and the second largest study ever conducted of its kind.

In 1986, IARC made the following comments regarding the epidemiological evidence for the reported association between ETS exposure and lung cancer (IARC, 1986): "Several epidemiological studies have reported an increased risk of lung cancer in nonsmoking spouses of smokers, although some others have not . . . The resulting errors could arguably have artifactually depressed or raised estimated risks, and, as a consequence, each is compatible either with an increase or with an absence of risk." It was on the basis of that conclusion that IARC decided to undertake its multi-center study. The results, based on an analysis of 650 cases and 1,542 controls in 12 centers in 7 European countries, were as follows:

- RR for spousal exposure -- 1.16 (95% CI, 0.93-1.44)
- RR for workplace exposure -- 1.17 (95% CI, 0.94-1.45)
- RR for combined exposure -- 1.14 (95% CI, 0.88-1.47)

The report also states that there was no evidence of an association between lung cancer risk and ETS exposure during childhood.

The two immediate conclusions that can be drawn from these results are that both indices of ETS exposure, spousal and workplace, suggest a small but positive association with lung cancer, but neither association is statistically significant. What cannot be determined from the results as presented is the extent to which they have been corrected for known systematic biases -- in particular, misclassification of smoking habit and confounding by diet (spousal exposure only). The most recent meta-analysis carried out on the possible association of ETS exposure and lung cancer (Hackshaw et al., 1997) arrived at a combined relative risk of 1.24, which the authors estimated should have been reduced by 0.06 for misclassification of smoking habit and by 0.02 for dietary confounding. Although their suggested reduction is almost certainly inadequate, accepting even these values would yield a reduction of 33% for the spousal exposure risk estimate in the IARC study, resulting in a relative risk of 1.10, and a reduction of 25% for the workplace exposure estimate, resulting in a relative risk of 1.13. Although these values are, of course, still greater than 1.0, it is as likely that they suggest no association whatsoever, as it is likely that they suggest an association.

However, it should be noted that the results reported by IARC are in line with other studies and, in particular, in line with a number of meta-analyses. Therefore, clearly, a possible interpretation of these results is that they confirm an association between reports of ETS exposure and lung cancer, although the association is extremely weak. It is worth noting that the Introduction

to the brief text in the IARC Biennial Report states that ETS exposure is a "likely cause" of lung cancer. This is a far less conclusive statement than made by some other agencies and scientists.

There are several interesting points that were made in the discussion of these results in the IARC Biennial Report. The first deals with dose-response trends, where the claim is made that "several quantitative indicators of ETS exposure showed a dose-response relationship with lung cancer risk." It is impossible to analyze this statement from the data provided in the summary; however, the fact that not all such indicators showed a dose-response relationship suggests that such an analysis would be of great importance.

Secondly, IARC states that: "A further study of non-smoking women in Moscow, Russian Federation, confirmed the results on ETS of the larger international investigation and suggested a role of environmental air pollution independent of the effect of ETS." In actuality, the results of this study (Zaridze et al., 1998) "confirm" only the result for spousal exposure. The authors report no increase in lung cancer risk for workplace exposure; moreover, the reported dose-response effects were negative, whether years of exposure or number of cigarettes smoked by the spouse was used as the metameeter of spousal exposure.

Lastly, the IARC summary states that: "In a separate exercise, the number of lung cancers occurring in the countries of the European Union that can be attributed to spousal ETS exposure was estimated to be about 800 among women and 300 among men." The reader is likely to assume that the calculation referred to utilized the relative risk of 1.16 obtained from the IARC

multi-center study. However, in actuality the authors of the paper used a relative risk for spousal exposure of 1.30, almost two times the uncorrected IARC result (Trédaniel et al. 1997).

## References

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